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Echocardiography

Mitral Valve Prolapse in the General Population

The Benign Nature of Echocardiographic Features in the Framingham Heart Study

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OBJECTIVES The aim of this study was to examine the echocardiographic features and associations of mitral valve prolapse (MVP) diagnosed by current two-dimensional echocardiographic criteria in an unselected outpatient sample.

BACKGROUND Previous studies of patients with MVP have emphasized the frequent occurrence of echocardiographic abnormalities such as significant mitral regurgitation (MR) and left atrial (LA) enlargement that are associated with clinical complications. These studies, however, have been limited by the use of hospital-based or referral series.

METHODS We quantitatively studied all 150 subjects with possible MVP by echocardiography and 150 age- and gender-matched subjects without MVP from the 3,491 subjects in the Framingham Heart Study. Based on leaflet morphology, subjects were classified as having classic ($n = 46$), nonclassic ($n = 37$), or no MVP.

RESULTS Leaflet length, MR degree, and LA and left ventricular size were significantly but mildly increased in MVP ($p < 0.0001$ to 0.004), with mean values typically within normal range. Average MR jet area was 15.1 ± 1.4% (mild) in classic MVP and 8.9 ± 1.5% (trace) in nonclassic MVP; MR was severe in only 3 of 46 (6.5%) subjects with classic MVP, and LA volume was increased in only 8.7% of those with classic MVP and 2.7% of those with nonclassic MVP.

CONCLUSIONS Although the echocardiographic characteristics of subjects with MVP in the Framingham Heart Study differ from those without MVP, they display a far more benign profile of associated valvular, atrial, and ventricular abnormalities than previously reported in hospital- or referral-based series. Therefore, these findings may influence the perception of and approach to the outpatient with MVP. (J Am Coll Cardiol 2002;40:1298–304) © 2002 by the American College of Cardiology Foundation

Mitral valve prolapse (MVP) has been described as the most common cardiac valvular abnormality in industrialized countries (1) and the leading cause of mitral valve surgery for isolated mitral regurgitation (MR) (2). Previous studies have emphasized the frequent occurrence of echocardiographic abnormalities in patients with MVP, including thickened and elongated leaflets with important MR and left heart chamber enlargement. These abnormalities, in turn, have been associated with clinical complications in as many as 10% to 46% of patients in those series, including congestive heart failure, mitral valve surgery, bacterial endocarditis, arrhythmias, and sudden death (3–19). Those studies, however, have been limited by the use of hospital-based or highly selected referral samples more likely to have echocardiographic and clinical abnormalities, similar to the experience with referral populations in hypertrophic cardiomyopathy (20,21). This perception of disease severity has affected individuals receiving the diagnosis, increasing personal and professional anxiety concerning the risk of complications and the need for prophylaxis.

A contrasting impression is that MVP is a common disorder (22–31), often affecting individuals who otherwise appear healthy (32,33). This impression, however, may relate to prior use of M-mode or two-dimensional (2-D) echocardiographic views nonspecific for the diagnosis of MVP (23,31,34–38). Recent understanding of the three-dimensional nonplanar shape of the mitral annulus (39–45) has allowed us to refine the 2-D echocardiographic criteria for MVP to minimize false positive diagnoses (46,47). To date, however, no study has applied these criteria to a community-based sample to characterize the echocardiographic manifestations of MVP. Therefore, this study examined the echocardiographic features of MVP as diag-

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Abbreviations and Acronyms

2-D	= two-dimensional
LA	= left atrial/atrium
LV	= left ventricle/ventricular
LVIDd	= left ventricular internal diameter in end-diastole
LVIDs	= left ventricular internal diameter in end-systole
MR	= mitral regurgitation
MVP	= mitral valve prolapse

nosed by current 2-D echocardiographic criteria in an unselected outpatient sample, as provided by the Framingham Heart Study.

METHODS

Study sample. The Framingham Heart Study was established in 1948 as a prospective epidemiologic cohort investigation. Offspring of the original cohort and the spouses of offspring were entered into a prospective study in 1971 (48,49). Subjects who participated in the fifth offspring examination (1991 to 1995) were the focus of this study. The examination protocol was approved by the Boston Medical Center Institutional Review Board, and all subjects gave informed consent.

The study sample consisted of all 3,491 subjects at the fifth offspring examination (1,845 women, 1,646 men) with technically adequate 2-D echocardiograms (245 subjects were eliminated because of technically inadequate echocardiograms for evaluating the mitral valve). Of this cohort, five subjects had a history of mitral valve repair or replacement, four of whom had documented pathologies other than MVP (mitral stenosis, ischemic MR). Only one subject had mitral valve surgery (repair) for MVP. These subjects were excluded from echocardiographic analysis because the measured variables could have been altered by the surgical intervention. To ensure complete ascertainment of MVP, we examined the echocardiograms of all subjects who were previously identified as having possible leaflet displacement suggesting prolapse in any 2-D view or by M-mode at any study exam (offspring exams 2,4,5). This broad-net approach identified 518 subjects. First, we assessed the fifth-examination echocardiograms of these 518 subjects to identify those in whom approach of the leaflets toward the annulus or qualitative superior systolic mitral leaflet displacement warranted quantitative evaluation to determine whether prolapse was actually present. Cases identified in this way (n = 150) were paired with age- and gender-matched control subjects drawn from the fifth offspring exam who were initially coded as having no evidence of MVP. Echocardiograms of cases and control subjects were examined blinded to MVP status and clinical history.

Echocardiographic methods. All subjects underwent standard 2-D echocardiograms with a commercially available system (Hewlett-Packard Sonos 1000, Andover, Massachusetts) using a 2.5-MHz transducer. Images were recorded on videotape, including complete parasternal, apical, and subcostal views, and color Doppler to assess valvular regurgitation. All measurements were performed using a Sony Off-Line Cardiac Analysis System (Sum 1010, Sony, Park Ridge, New Jersey).

Using current 2-D echocardiographic criteria based on the three-dimensional shape of the annulus and clinical correlations (14,39–47), the diagnosis of MVP was made by measurement of maximal mitral leaflet superior systolic displacement relative to the line connecting the annular hinge points. Displacement of the anterior and posterior mitral leaflets was measured in the parasternal and apical long-axis views, which were scanned by tilting the transducer to visualize the medial, central, and lateral scallops of the posterior leaflet (14,39,40,46,47). Because the lateral scallop of the posterior leaflet is most difficult to evaluate from these views, and in order to ensure its complete assessment, its displacement was also measured in the apical four-chamber view (46,50); however, such displacement could always be confirmed in the long-axis scans. Mitral leaflet thickness in diastasis was measured as the leading to trailing edge of the thickest area of the midportion of the leaflet, excluding focal areas of thickness and chordae (4,14,46,51,52). Each leaflet was measured, and maximal thickness was used for categorization. On the basis of prior clinical and prognostic studies, subjects were classified as having classic MVP (displacement >2 mm, thickness ≥ 5 mm) or nonclassic MVP (displacement >2 mm, thickness <5 mm) (4,5,14,46,47). Borderline degrees of displacement (≤ 2 mm) have been shown to lack association with increased leaflet thickness, MR, left atrial (LA) enlargement, valve-related complications, or progression over 10 years and were not included as prolapse (46).

Maximal mitral annular diameter was measured at end-systole as the length of the line connecting the midportion of the leaflet hinge points in the parasternal long-axis view (51). The lengths of the anterior and posterior mitral leaflets were traced in diastasis in the parasternal long-axis view from their hinge points to the free edges along the middle of the leaflets, excluding the chordae (51). The degree of MR was assessed as maximal regurgitant jet area/LA area ratio in the parasternal and apical long-axis and apical four-chamber views (53). Trace, mild, moderate, and severe MR were classified on the basis of jet area/LA area ratios of $>0\%$ to 10%, $>10\%$ to 20%, $>20\%$ to 40%, and $>40\%$ (53).

Three maximal end-systolic LA dimensions were measured: the anteroposterior diameter obtained in the parasternal long-axis view at the aortic leaflet insertion points; and the mediolateral and inferosuperior diameters obtained in the apical four-chamber view and passing through the midpoint of the visualized atrial area (46). Left atrial volume was calculated as the product of these dimensions $\times \pi/6$ to give the volume of an ellipsoid (46). Left ventricular internal diameter in end-systole (LVIDs) and left ventricular internal diameter in end-diastole (LVIDd) were measured in the

Table 1. Mitral Valve Features and Associated Echocardiographic Features of MVP

	Classic MVP (n = 46)	Nonclassic MVP (n = 37)	No MVP (n = 217)	p Value*
Maximal leaflet displacement (mm)	3.8 ± 1.0	3.1 ± 0.6	−0.5 ± 2.0	NA
Maximal leaflet thickness (d) (mm)	5.6 ± 0.1	4.3 ± 0.1	3.6 ± 0.1	NA
Anterior leaflet thickness (d) (mm)	5.0 ± 0.1	3.9 ± 0.1	3.3 ± 0.04	NA
Posterior leaflet thickness (d) (mm)	5.6 ± 0.1	4.1 ± 0.1	3.4 ± 0.1	NA
Anterior leaflet length (mm)	23.9 ± 0.4	22.2 ± 0.5	19.3 ± 0.2	0.0001
Posterior leaflet length (mm)	15.0 ± 0.2	14.0 ± 0.3	12.2 ± 0.1	0.0001
Mitral annular diameter (mm)	34.5 ± 0.4	32.0 ± 0.5	29.1 ± 0.2	0.0001
Mitral regurgitation (%)	15.1 ± 1.4 (mild)	8.9 ± 1.5 (trace)	2.4 ± 0.6 (trace)	0.0001
Mitral annular calcification†	11 (20.4)	7 (17.5)	11 (4.5)	0.0001
Papillary muscle tug	15 (33.0)	11 (30.0)	1 (0.4)	0.0001
Posterior wall motion	44 (95.4)	36 (100)	60 (26.5)	0.0001

Maximum leaflet displacement is expressed as an unadjusted mean ± standard deviation. All other measurements (least squares means ± standard errors) are adjusted for age, gender, and body mass index, except mitral annular diameter which was also adjusted for height. *p values compare classic MVP + nonclassic MVP versus no MVP. †Mitral annular calcification was considered significant if moderate or severe.

d = diastole; MVP = mitral valve prolapse; NA = not applicable because measurements differ by group definition.

parasternal long-axis view below the mitral leaflet tips as recommended by the American Society of Echocardiography (54). Left ventricular ejection fraction was calculated as follows: $([LVIDd^2 - LVIDs^2]/LVIDd^2) \times 100 + 10\%$ for a normal apex, as all subjects had a normal apex (55).

All measurements, except jet and LA area, were made in the same view on two separate cardiac cycles that provided unambiguous identification of the structures, and the two values were averaged. No measurements were made on premature or post-premature atrial or ventricular beats. The intraobserver (L. A. F.) and interobserver (L. A. F. and R. A. L.) correlations for mitral leaflet displacement, leaflet thickness, and degree of MR in 20 subjects exceeded 0.97.

Associated echocardiographic features. Other echocardiographic features associated with MVP that were assessed included mitral annular calcification/thickening, papillary muscle tug or superior traction, and exaggerated posterior wall motion. Mitral annular calcification was classified in the parasternal short-axis view as absent, mild (focal), moderate (calcification of one-third of the mitral annular ring), or severe (calcification of at least one-half of the mitral annular ring) (56). The classification of mitral annular calcification was confirmed qualitatively on the parasternal long-axis and apical four-chamber views for extent of calcification and thickening. Papillary muscle superior traction or tug was defined as exaggerated superior motion of the papillary muscle toward the mitral annulus during systole, in parallel with the superior leaflet displacement (57). The posterior mitral annulus and adjacent left ventricular (LV) wall were examined for exaggerated inward systolic motion in the parasternal and apical long-axis views.

Statistical methods. Analysis of covariance (58) was used to test for differences between subjects with and without MVP on continuous echocardiographic variables. Least squares means and standard errors are presented. Logistic regression analysis (59) was used to test for differences between subjects with and without MVP in the dichotomous echocardiographic variables. Left atrial and LV chamber sizes, LA volume, and mitral annular diameter were adjusted for age, gender, height, and body mass index. The following variables were adjusted for age, gender, and body mass index: mitral leaflet thicknesses and lengths, degree of MR, LV ejection fraction, mitral annular calcification, papillary muscle tug, and exaggerated posterior wall motion. All comparisons were made by pooling subjects with classic and nonclassic MVP and comparing the pooled sample with those without MVP. This was an a priori decision made because of the relatively small sample size of those with prolapse. A two-sided p value of <0.05 was the criterion for statistical significance. All analyses were conducted using SAS (60) on a Sun Ultrasparc Workstation (Sun Microsystems, Santa Clara, California).

RESULTS

Diagnosis of MVP. By quantitative evaluation, 46 subjects had classic MVP and 37 had nonclassic MVP. The remaining subjects did not meet quantitative criteria for MVP, including all 150 matched subjects whose initial qualitative evaluation did not suggest MVP (61).

Age and gender. The mean age was 56.7 ± 1.5 years (gender-adjusted least squares mean ± standard error) for those with classic MVP, 55.4 ± 1.6 years for those with nonclassic MVP, and 54.7 ± 0.2 years for those without MVP (p = 0.19). The age range for the overall sample was 26 to 84 years. The gender distribution among subjects with classic and nonclassic MVP versus those without MVP was similar; 60% of subjects with MVP were female versus 53% of those without MVP (p = 0.21) (61).

Leaflet and annular measures. Echocardiographic features associated with MVP are reported in Table 1. Anterior mitral leaflet length was mildly increased in subjects with nonclassic and classic MVP compared with those without MVP (Table 1), but mean values did not exceed the range of 21 to 24 mm reported in the anatomic (62,63) or echocardiographic (64) literature for normal subjects. Posterior leaflet length was greater in those with MVP, with the average rising above the reported normal range of 12 to

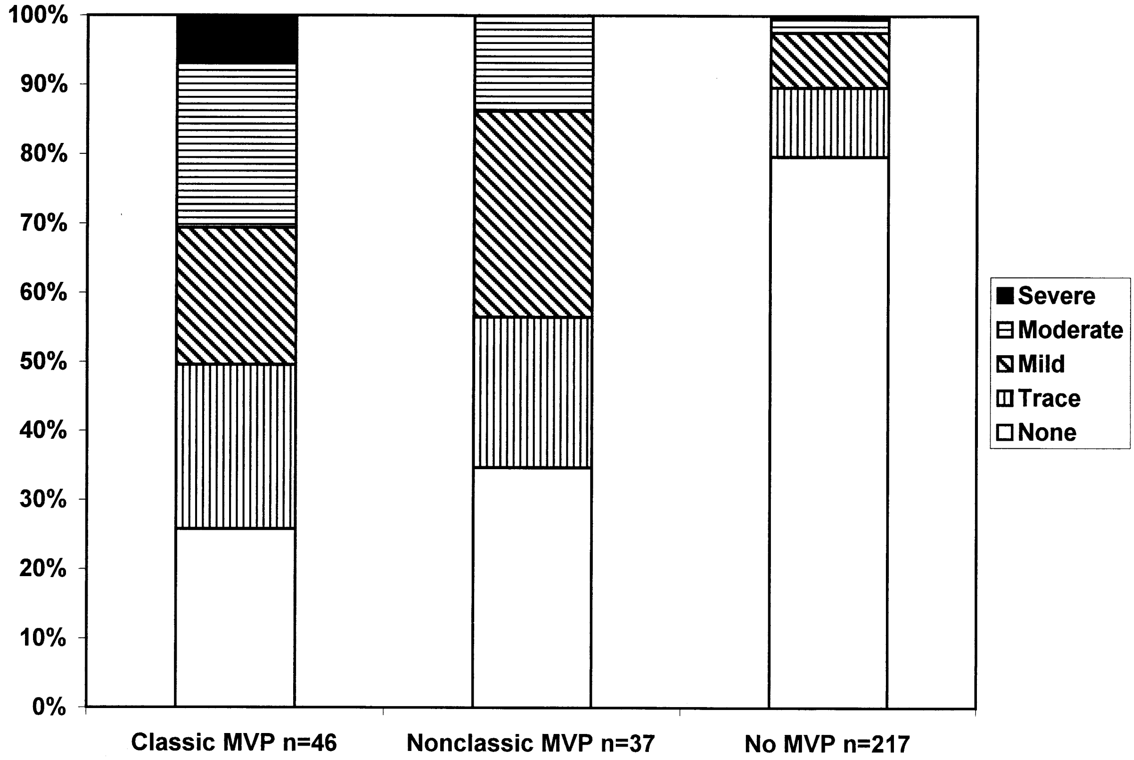

Figure 1. The distribution of mitral regurgitation severity among the subjects in the study. MVP = mitral valve prolapse.

14 mm only for the classic group. In addition, mitral annular diameter was increased in those with MVP. The subjects with MVP had a higher prevalence of significant mitral annular calcification than those without MVP. Papillary muscle tug or superior traction occurred almost exclusively in subjects with MVP. Exaggerated posterior LV wall motion occurred in almost all patients with MVP, but was also seen in 26.5% of those without MVP.

MR. The extent of MR was significantly higher in subjects with versus those without MVP, but the average percent jet area was only 15.1 (mild MR, Table 1) in those with classic MVP and 8.9 (trace MR) in those with nonclassic MVP. In the classic group, only 3 of 46 subjects (6.5%) had severe MR by Doppler color flow mapping. There were no subjects with severe MR in the nonclassic group, and one, or 0.5%, in those without MVP. The vast majority of subjects were only mildly affected: 70% of subjects in the classic group had no, trace, or mild MR, as did 86% of those with nonclassic MVP and 98% of those without MVP (Fig. 1).

LA and LV measures. Adjusting for age, gender, height, and body mass index, LA anteroposterior and mediolateral diameters, LA volumes, and LVIDd were significantly but mildly higher in subjects with MVP compared with subjects without MVP (Table 2). However, the vast majority of subjects with MVP had dimensions within the range of normal with few rising above them (65,66) (Table 3). Indexing chamber dimensions for height did not cause substantive differences in the results. Left atrial size correlated with MR in the mediolateral (r = 0.22) and anteroposterior (r = 0.26) dimensions; LA anteroposterior diameter was increased in 4 of 24, or 17%, subjects with moderate to severe MR versus 5 of 276, or 1.8%, of those

Table 2. Features of LA and LV Chambers

	Classic MVP (n = 46)	Nonclassic MVP (n = 37)	No MVP (n = 217)	p Value*
LA diameter (ap) (cm)	3.29 ± 0.04	3.09 ± 0.05	3.00 ± 0.02	0.0001
LA diameter (ml) (cm)	3.98 ± 0.07	3.77 ± 0.07	3.61 ± 0.03	0.0001
LA diameter (is) (cm)	4.83 ± 0.08	4.57 ± 0.09	4.70 ± 0.04	0.99
LA volume (cm^3)	33.6 ± 1.0	28.3 ± 1.1	27.0 ± 0.5	0.0001
LVIDd (cm)	4.63 ± 0.04	4.40 ± 0.05	4.40 ± 0.02	0.0038
LVIDs (cm)	2.92 ± 0.04	2.78 ± 0.05	2.78 ± 0.02	0.03
LV ejection fraction (%)	70.0 ± 0.9	69.4 ± 1.0	69.8 ± 0.4	0.84

All measurements (least squares means ± standard errors) are adjusted for age, gender, height, and body mass index, except ejection fraction which was not adjusted for height. *p values compare classic MVP + nonclassic MVP versus no MVP.

ap = anteroposterior; is = inferosuperior; LA = left atrial; LV = left ventricular; LVIDd = left ventricular internal diameter in end-diastole; LVIDs = left ventricular internal diameter in end-systole; ml = mediolateral; MVP = mitral valve prolapse.

Table 3. Proportion of Increased LA and LV Measures

	Classic MVP (n = 46) (%)	Nonclassic MVP (n = 37) (%)	No MVP (n = 217) (%)
Increased LA diameter (ap) (cm)	3 (6.5)	0 (0)	6 (2.8)
Increased LA diameter (ml) (cm)	5 (11)	1 (2.7)	1 (0.5)
Increased LA volume (cm^3)	4 (8.7)	1 (2.7)	3 (1.4)
Increased LVIDd (cm)	3 (6.5)	0 (0)	0 (0)

Reference values: LA diameter (ap) ≤ 3.8 cm; LA diameter (ml) ≤ 4.7 cm; LA volume ≤ 46 cm^3; LVIDd ≤ 5.3 cm.
Abbreviations as in Table 2.

with none, trace, or mild MR. Ejection fraction was not different among the groups.

DISCUSSION

Mitral valve prolapse can be clearly identified by echocardiography in a community-based sample, with superior leaflet displacement and increases in leaflet thickness, leaflet length, and MR. Nevertheless, these echocardiographic features and associations, although significant, are relatively mild. Severe MR is uncommon, and the vast majority, even of those with thickened leaflets, have no, trace, or mild MR. Left atrial size is similarly only mildly increased in these subjects with MVP, with average values that lie within the normal range; atrial size lies above this range in only a small proportion of those with classic MVP and thickened leaflets. Leaflet length lies within or only slightly above the normal range described in anatomic and echocardiographic series in the classic group (62–64) and is within the normal range in the nonclassic group. Anterior leaflet length lies well below the 29 mm associated with congestive heart failure and the 26 mm associated with sudden death in a recent autopsy series (15). Left ventricular dysfunction is absent, and mild LV dilation rarely present. Therefore, the MVP is a definable entity, but with relatively benign echocardiographic manifestations in a general outpatient population.

Comparison with previous literature. Previous studies of MVP have often focused on echocardiographic abnormalities and their association with clinical complications (3–19). Tresch et al. (6), for example, found dilated LA and LV in 90% of patients with MVP requiring mitral valve repair. In a large series of subjects with MVP, Zuppiroli et al. (16) found a high likelihood of complications, including cardiac death, and mitral valve replacement from progressive MR, in patients with enlarged LA and LV. Studies emphasizing complications, however, have generally used hospital-based or referral samples, increasing the likelihood of finding echocardiographic and clinical abnormalities (16).

A different picture emerges from this study of an unselected outpatient sample. The subjects with MVP in this population did, in fact, have echocardiographic abnormalities, consistent with prior studies (4,5,9,14,15,40,67). These findings, however, were typically mild, uncommonly exceeding the normal range or increasing to the levels seen in patients with complications. (Only one patient in this cohort has needed mitral valve repair for important MR with atrial fibrillation.) Therefore, even when MVP is diagnosed with the more specific criteria currently used—which would be expected to enrich for patients with definite abnormalities—there is a relatively benign constellation of associated findings. As in the case with hypertrophic cardiomyopathy, this reflects study design: studies at referral institutions suggest a frequently symptomatic disease with a high rate of complications, whereas eliminating such patient referral and selection biases in outpatient samples can dramatically change the perception of disease (20,21).

Features associated with MVP. Mitral annular calcification occurred more frequently in Framingham subjects with MVP. It has been associated with both MR and MVP (68–70) and ascribed to increased mitral leaflet stress related to abnormal motion. It should be noted that echogenic appearances are nonspecific for calcification (71), however, and may represent annular thickening related to the myxomatous process. Papillary muscle superior tug occurred almost exclusively in subjects with important leaflet displacement, as in the prior literature (57). Clinically, it has yet to be demonstrated that such traction increases the propensity for lethal arrhythmias, as it does experimentally (72). Exaggerated inward posterior wall motion has been previously reported (70) but is not well understood; one potential mechanism would be traction by mural or other chordae on the adjacent myocardium. These findings, especially the abnormal papillary muscle and myocardial motion, are currently of greatest value as visual cues to heighten the awareness of the echocardiographer to the possibility of MVP.

Study limitations. Although the overall study sample was large, the total number of subjects with MVP was modest. Nevertheless, the purpose of the study was achieved, namely, to examine the echocardiographic features and associations of MVP in an unselected outpatient sample. Unlike studies of patients seeking medical attention for complications of MVP or concerns regarding it, this study seeks to characterize MVP in the community, which has not been well described; this difference in population can explain differences in the apparent severity of presentation. In addition, the sample was predominantly Caucasian and it is possible that the results may not be generalized to other ethnic and racial groups. This study was cross-sectional, and additional studies are exploring progression. Of note is the fact that the single individual with MVP who required surgical repair before the study was excluded from the analysis for LA and LV size because they were not available in a comparable unoperated state at the same time that other subjects were studied. This may slightly skew these dimensions. Finally, we used the jet/LA area ratio as the best available quantitative measure at the time the echoes were obtained (53). This single-frame measure may, for example, overestimate MR that is limited to late systole, compared with more recent quantitative and integrated assessments

(73). However, comparison with the routine semiquantitative grading done independent of this MVP study, which integrates multiple aspects of jet size over time in several views, showed no major over- or underestimation.

Summary and clinical implications. We combined an unselected study sample and current 2-D echocardiographic criteria for the diagnosis of MVP to explore the echocardiographic features of MVP in the community. We found that although the subjects with MVP in the Framingham Heart Study are significantly different from those without MVP in the defining and classifying features of leaflet displacement and thickness, they display a far more benign profile of associated valvular, atrial, and ventricular abnormalities than previously reported in hospital- or referral-based series. This profile of echocardiographic abnormalities such as MR and LA enlargement, which is associated with clinical complications, establishes the perception of disease severity, and a low frequency may allay anxiety for the individual diagnosed with MVP in the general outpatient setting. The frequent presence of no or trace MR in subjects with MVP is also relevant in considerations regarding antibiotic prophylaxis and in balancing its potential risks and benefits (74,75). As in studies of hypertrophic cardiomyopathy, the common theme is emerging that the profile of disease in patients with severe symptoms and demonstrated complications is not applicable to most individuals diagnosed by screening or routine evaluation in the general population, whose findings are far more benign.

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